REMARKS

With entry of the amendment, claims 1-53 are pending in the application. Claims 35-47 have been withdrawn from consideration; claims 3 and 17, which the Examiner characterized as being drawn to a non-elected species, were not considered. Claims 11-13 stand rejected under 35 U.S.C. 112, second paragraph, and claims 1, 2, 9-16, 21, 24-28, and 31-34 stand rejected under 35 U.S.C. 103(a).

In view of the amendments above and the arguments below, Applicants respectfully request reconsideration on the merits of the application and allowance of the claims.

New claims

New claims 48 and 49 depend from claim 4, and require that at least one mononucleotide repeat locus includes MONO-15 or MONO-11, respectively. Claim 50 is an independent claim that combines all of the limitations of claims 1-4. Claims 51 and 52 depend from claim 50, and require that at least one mononucleotide repeat locus includes MONO-15 or MONO-11, respectively. Claim 53 is an independent claim that combines all of the limitations of claims 1, 2, and 4. Claims 54 and 55 depend from claim 53, and require that at least one mononucleotide repeat locus includes MONO-15 or MONO-11, respectively.

Rejections under 35 U.S.C. 112, second paragraph

Claims 11-13 stand rejected as being incomplete for omitting essential steps. Each claim depends from claim 10 and is drawn to a method of analyzing micro-satellite instability, wherein at least one sample of genomic DNA comprises DNA from normal non-cancerous biological material from an individual, and a second sample comprises genomic DNA from a tumor of the individual. The Examiner asserted that an essential step is missing that results in a gap between the final step and the preamble to the claim. Applicants have amended claims 11-13 for reasons unrelated to patentability to better clarify the invention. Applicants request that the rejection under 35 U.S.C. 112, second paragraph be withdrawn.

Rejections under 35 U.S.C. 103(a)

Claims 1, 2, 9-16, 21, 24-28, and 31-34 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Ruschoff et al. (U.S. Patent No. 6,150,100) in view of Schumm et al. (U.S. Patent No. 5,843,660). Claims 4-18, 20, 22, 23, 29, and 30 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Ruschoff et al. (U.S. Patent No. 6,150,100) in view of Schumm et al.

(U.S. Patent No. 5,843,660), further in view of Kieback (U.S. Patent No. 5,645,995) and Sulston et al. (Genome Res. 8:1097-1108, sequence alignment from GenEmbl).

The Examiner characterized Ruschoff et al. as disclosing a method of determining microsatellite instability at selected microsatellite loci by amplifying the microsatellite loci using primers for each set of micro-satellite loci comprising mono-, di-, tetra-, or pentanucleotide repeat loci; the Examiner acknowledged that Ruschoff et al. does not teach multiplex amplification.

Schumm et al. is characterized as teaching multiplex amplification of short tandem repeat loci comprising co-amplifying at least three tandem repeat loci from one or more DNA samples and determining the size of the amplified alleles. Schumm et al. is further characterized as disclosing that three or more, or even as many as eight or more loci can be co-amplified in a single amplification reaction.

Kieback is cited as teaching a method for diagnosing an increased risk for breast or ovarian cancer, and as disclosing "a primer sequence" (SEQ ID NO:5, column 5, lines 11-12) comprising the MONO-15 primer (SEQ ID NO:8) of the instant application.

Sulston et al. is said to teach a sequence of *Homo sapiens* BAC clone (sequence alignment from GenEmbl database) comprising a MONO-15 primer (SEQ ID NO:7). The reverse complement of bases 79-96 of SEQ ID NO:5 of the Kieback patent is identical to SEQ ID NO:8 of the present invention, and SEQ ID NO:7 matches a sequence from human chromosome 5 (clone RP11-323C17 T7 end).

Applicants believe that including claims 31-34 in the group of claims rejected over the combination of Ruschoff et al. and Schumm et al. was an error. Claims 31-34 depend from claim 29 and, therefore, require amplification of at least one mono-nucleotide repeat locus selected from the group consisting of MONO-11 and MONO-15. Only Kieback and Sulston et al. are cited as teaching a MONO-15 primer sequence. Therefore, Applicants will address the rejection of claims 31-34 together with the rejection of claims 29 and 30.

Rejection of claims 1, 2, 9-16, 21, and 24-28

The Examiner asserts that the ordinary practitioner would have been motivated to combine the teachings of Ruschoff et al. and Schumm et al. in order to achieve the expected advantage of a rapid and sensitive method for detecting microsatellite instability.

A prima facie case of obviousness requires: (1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) a reasonable expectation of

success; and (3) the art reference or combination of references must teach all of the claim limitations (MPEP 2142). The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) (MPEP 2143). Applicants respectfully submit that the Examiner has failed to establish a prima facie case of obviousness because the prior art does not teach all of the claim limitations, there is no motivation to combine the prior art teachings, and even if one were motivated to combine the prior art teachings, the art does not provide a reasonable expectation of success.

Independent claims 1 and 15 are reproduced below. Claims 2 and 9-14 depend from claim 1, and claims 16, 21, and 24-28 depend from claim 15.

1. A method of analyzing micro-satellite loci, comprising steps of:

a) providing primers for co-amplifying a set of at least three microsatellite loci of genomic DNA, comprising at least one mono-nucleotide repeat locus and at least two tetra-nucleotide repeat loci;

b) co-amplifying the set of at least three microsatellite loci from at least one sample of genomic DNA in a multiplex amplification reaction, using the primers, thereby producing amplified DNA fragments; and

c) determining the size of the amplified DNA fragments.

15. A method of detecting microsatellite instability in genomic DNA, comprising the steps of:

a) providing primers for co-amplifying a set of at least three microsatellite loci of genomic DNA, comprising at least one mono-nucleotide repeat locus and at least two tetra-nucleotide repeat loci;

b) co-amplifying the set of at least three microsatellite loci from a first sample of genomic DNA originating from normal non-cancerous biological material from an individual and a from a second sample of genomic DNA originating from a second biological material from the individual, in separate multiplex amplification reactions; using the primers, thereby producing first amplified DNA fragments from the first sample and second amplified DNA fragments from the second sample; and

c) comparing the size of first amplified DNA fragments to the size of the second amplified DNA fragments to detect instability in any of the at least three microsatellite loci of the second genomic DNA.

Although Ruschoff et al. discloses amplifying various mono-, di-, tetra-, or pentanucleotide repeat loci to assess their value in detecting microsatellite instability, the Examiner notes that Ruschoff et al. does not teach a method of analyzing or detecting microsatellite instability comprising co-amplifying at least three microsatellite loci comprising at

least one mononucleotide repeat locus and at least two tetranucleotide loci, as required by claims 1-28.

Schumm et al. teaches co-amplifying short tandem repeat (STR) loci, which are defined as regions of the human genome containing short repetitive sequence elements of 3 to 7 bases pairs in length (Schumm et al., column 12, lines 27-29). In contrast, the methods of claims 1-28 of the subject application requires co-amplifying at least three microsatellite loci comprising at least one mononucleotide repeat locus and at least two tetranucleotide repeat loci.

Applicants submit that the ordinary practitioner wishing to reliably detect microsatellite instability using a limited number of PCR reactions would not be motivated to modify Ruschoff et al. to co-amplify at least two tetranucleotide repeat loci. In fact, Ruschoff et al. reported "pronounced heterogeneity with regard to each individual (tetranucleotide repeat) locus" (Ruchsoff et al., column 7, lines 44-47; Fig. 3). Heterogeneity is undesirable because it reduces utility of that loci in prognosis.

Applicants submit that neither Ruschoff et al. nor Schumm et al. suggests or provides motivation to modify or combine the references to make a method of analyzing microsatellite loci comprising co-amplifying at least one mononucleotide repeat locus and at least two tetranucleotide repeat loci, as required by claims 1 and 15, and their dependent claims 2, 9-14 16, 21, and 24-28. Furthermore, the cited references do not provide a reasonable expectation of success of the methods as claimed.

Rejection of claims 4-8, 18-20, 22, 23, and 29-34

Claims 4-8, 18-20, 22, 23, 29, and 30 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Ruschoff et al. in view of Schumm et al., further in view of Kieback and Sulston et al. As noted above, Applicant will address the rejection of claims 31-34 together with the rejection of claims 29 and 30. Claim 1, from which claims 4-8 depend, and claim 15, from which claims 18-20, 22, and 23 depend, are reproduced above.

Claims 4-8, 18-20, 22 and 23 depend from claim 1 or 15.

Claim 4 requires at least one mono-nucleotide repeat loci selected from BAT-25, BAT-26, MONO-11, and MONO-15.

Claim 5 requires co-amplification of at least five microsatellite loci comprising at least two mono-nucleotide repeat loci selected from BAT-25, BAT-26, MONO-11, and MONO-15, and at least three tetranucleotide repeat loci selected from of FGA, D1S518, D1S547, D1S1677, D2S1790, D3S2432, D5S818, D5S2849, D6S1053, D7S3046, D7S1808, D7S3070, D8S1179,

D9S2169, D10S1426, D10S2470, D12S391, D17S1294, D17S1299, and D18S51.

Claim 6 requires that at least one of the primers has a nucleic acid sequence selected from SEQ ID NO:1-62.

Claim 7 requires co-amplification of at least nine microsatellite loci comprising BAT-25, BAT-26, MONO-11, MONO-15, D1S518, D3S2432, D7S1808, D7S3070, D7S3046, and D10S1426.

Claim 8, which depends from claim 7, uses primer pairs of SEQ ID NOs 1 and 60, 61 and 62, 7 and 8, 49 and 50, 17 and 59, 51 and 52, 53 and 54, 55 and 56, or 57 and 58 to amplify microsatellite loci BAT-25, BAT-26, MONO-15, D1S518, D3S2432, D7S1808, D7S3070, D7S3046, or D10S1426, respectively.

Claim 18, which depends from claim 15, at least one mono-nucleotide repeat loci selected from BAT-25, BAT-26, MONO-11, and MONO-15.

Claim 19, which depends from claim 16, requires co-amplification of at least five microsatellite loci comprising at least two mono-nucleotide repeat loci selected from BAT-25, BAT-26, MONO-11, and MONO-15, and at least three tetranucelotide repeat loci selected from of FGA, D1S518, D1S547, D1S1677, D2S1790, D3S2432, D5S818, D5S2849, D6S1053, D7S3046, D7S1808, D7S3070, D8S1179, D9S2169, D10S1426, D10S2470, D12S391, D17S1294, D17S1299, and D18S51.

Claim 20, which depends from claim 16, requires that at least one of the primers has a nucleic acid sequence selected from SEQ ID NO:1-62.

Claim 22, which depends from claim 16, requires co-amplification of at least nine microsatellite loci, nine of which loci are specifically recited.

Claim 23, which depends from claim 22, uses primer pairs of SEQ ID NOs 1 and 60, 61 and 62, 7 and 8, 49 and 50, 17 and 59, 51 and 52, 53 and 54, 55 and 56, or 57 and 58 to amplify microsatellite loci BAT-25, BAT-26, MONO-15, D1S518, D3S2432, D7S1808, D7S3070, D7S3046, or D10S1426, respectively.

Independent claim 29, from which claims 30-34 depend, is reproduced below.

29. A method of analyzing at least one mono-nucleotide repeat locus, comprising the steps of:

a) providing at least one primer for at least one mono-nucleotide repeat locus of human genomic DNA selected from the group consisting of MONO-11 and MONO-15;

b) amplifying at least one mono-nucleotide repeat locus from a sample of genomic DNA originating from a biological material from an individual, using the at least one primer, thereby producing amplified DNA fragments; and

d) determining the size of the amplified DNA fragments.

Claim 30 requires that the mononucleotide repeat locus is amplified using at least one primer selected from the group consisting of SEQ ID NO:5-8.

The Examiner cited Ruschoff et al., Schumm et al., Kieback, and Sulston et al. for the reasons set forth above.

Kieback discloses that point mutations in EXON 4 or EXON 5 of the progesterone receptor gene were associated with an Alu insertion (SEQ ID NO:5) in INTRON G, and are correlated with increased risk for breast or ovarian cancer (col. 3, lines 62-67; col. 5, lines 11-12, and SEQ ID NO:5). In contrast to the Examiner's characterization that Kieback teaches "a primer comprising SEQ ID NO:8 of the present invention", Kieback discloses an Alu insertion (SEQ ID NO:5), and the reverse complement the of bases 79-96 of SEQ ID NO:5 is the same as SEQ ID NO:8 of the present invention. The mere existence of the sequence does not render obvious its use in amplifying mono-nucleotide repeat locus MONO-15 in a method of analyzing microsatellite repeat loci. Kieback teaches a correlation between the presence of an Alu insertion in INTRON G and point mutations in EXONS 4 and 5 of a particular gene. Kieback suggested that SEQ ID NO:5 could be used to detect the presence of an Alu insertion, but contains no discussion of the MONO-15 microsatellite locus, nor any suggestion that a primer comprising the reverse complement of bases 79-96 of SEQ ID NO:5 would be useful in amplifying the MONO-15 microsatellite locus, either alone or in combination with other microsatellite loci.

Similarly, the GenEmbl disclosure of a BAC clone sequence comprising a sequence identical to a MONO-15 primer (SEQ ID NO:7) does not teach or suggest amplifying MONO-15. There is nothing in the cited art to suggest that the sequences could be used as primers in PCR reactions to amplify a microsatellite locus. Furthermore, there is no suggestion to use SEQ ID NO:7 and SEQ ID NO:8 together as a primer pair, as required by claims 8 and 23.

Applicants respectfully submit that Ruschoff et al., Schumm et al., Kieback, and Sulston et al. do not combine to teach a method of co-amplifying at least one mononucleotide repeat locus and at least two tetranucleotide repeat loci, wherein the mononucleotide locus is selected from BAT-25, BAT-26, MONO-11, and MONO-15, as required by claims 4 and 18. Nor do the references combine to teach a method of co-amplifying at least two mononucleotide repeat loci selected from BAT-25, BAT-26, MONO-11, and MONO-15, and at least three tetranucleotide repeat loci selected from FGA, D1S518, D1S547, D1S1677, D2S1790, D3S2432, D5S818, D5S2849, D6S1053, D7S3046, D7S1808, D7S3070, D8S1179, D9S2169, D10S1426, D10S2470,

D12S391, D17S1294, D17S1299, and D18S51 as required by claims 5 and 19. Nothing in the art of record suggests co-amplifying at least one mononucleotide repeat locus and at least two tetranucleotide repeat loci using at least one primer having a nucleic acid sequence selected from SEQ ID NO:1-62, as required by claim 6 and 20, nor co-amplifying at least nine microsatellite loci comprising BAT-25, BAT-26, MONO-15, D1S518, D3S2432, D7S1808, D7S3070, D7S3046, and D10S1426, as required by claim 7 and 22. Further, the art of record does not combine to teach co-amplifying at least nine microsatellite loci using at least one primer pairs selected from SEQ ID NOs 1 and 60, 61 and 62, 7 and 8, 49 and 50, 17 and 59, 51 and 52, 53 and 54, 55 and 56, and 57 and 58 to amplify microsatellite loci BAT-25, BAT-26, MONO-15, D1S518, D3S2432, D7S1808, D7S3070, D7S3046, or D10S1426, respectively.

None of the cited references teaches the amplification of any of the particular tetranucleotide repeat loci recited in claims 5, 7, 19, or 22, let alone the co-amplification of particular combinations of at least three of the these loci, required in claims 5 and 19. Nor do the combination of references teach the co-amplification of at least nine microsatellite loci comprising BAT-25, BAT-26, MONO-15, D1S518, D3S2432, D7S1808, D7S3070, D7S3046, or D10S1426 of claims 7 and 22. Nothing in the art of record discloses co-amplifying the claimed tetranucleotide repeat loci to analyze microsatellite instability. The art of record therefore fails to teach all of the claim limitations and provides no reasonable expectation of success of the claimed invention. There is nothing in the art of record to point to the selection of the at least three tetranucleotide repeat loci required in claims 5 and 19, nor to the at least six tetranucleotide repeat loci required in claims 7 and 22.

None of the art of record discloses amplifying at least one mononucleotide repeat locus selected from the group consisting of MONO-11 and MONO-15, as required by claim 29-34, nor using at least one primer selected from the group consisting of SEQ ID NO:5-8 to amplify MONO-11 or MONO-15.

In view of the foregoing, Applicants respectfully request that the rejection of claims under 35 U.S.C. 103(a) be withdrawn.

As the application is now in condition for allowance, Applicants respectfully request withdrawal of the rejections and allowance of the claims. This response is being filed within four months of the mailing date of the Office Action, and is accompanied by a petition for a one-month extension of time, and by check No. 43995 in the amount of $110.00 for the extension of time fee. Check No. 43993 in the amount of $ 312.00 is enclosed to cover the cost of the new claims added by this amendment. No other fee is believed due in connection with this submission. If any

additional fee is due, please charge such fee to Deposit Account No. 50-0842.

Applicants invite the Examiner to contact the undersigned should he require further clarification concerning this response.

Respectfully submitted,

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MARKED-UP VERSION OF CLAIMS SHOWING CLEARLY THE AMENDMENTS

11. (Once amended) The method of claim 10, [wherein] further comprising correlating the microsatellite instability results [are used in prognostic tumor diagnosis the microsatellite instability results] with the prognosis.

12. (Once amended) The method of claim 10, [wherein] further comprising correlating the microsatellite instability results [are used in the diagnosis of] with familial tumor predisposition.

13. (Once amended) The method of claim 10, [wherein] further comprising correlating the microsatellite instability results [are used to detect] with the presence of cancerous tumors of the gastro-intestinal system and of the endometrium.